PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Improvements in or relating to the Production of Therapeutically Effective Derivatives of 4:4¹-Diamino Diphenyl Sulphone

We, ELI LILLY AND COMPANY of 740, South Alabama Street, Indianapolis, Indiana, United States of America, a Corporation organised and existing under the laws of the State of Indiana, United States of America, MORRIS SELIG KHARASCH, a Citizen of the United States of America, whose address is Jones Chemical Laboratory, University of Chicago, Chicago, Illinois, United States of America, and OTTO REINMUTH, a Citizen of the United States of America, whose address is Jones Chemical Laboratory, University of Chicago, Chicago, Illinois, United States of America, do hereby declare the nature of this invention and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

This invention is for improvements in or relating to the production of therapeutically effective compounds, and more particularly to the production of new derivatives of 4,4¹-diaminodiphenyl sulphone.

According to the present invention, this range of products is prepared by reacting 4,4¹-diaminodiphenyl sulphone with formaldehyde and with an N-acylcysteine, with or without subsequent reaction with a base to produce the corresponding salt. The said products may also be obtained, in accordance with this invention, by reacting an N-acylcrysteine with the product resulting from the interaction of 4,4¹-diaminodiphenyl sulphone and formaldehyde, with or without subsequent reaction with a base. The reaction may be carried out in a suitable medium in the presence of a small amount of a non-oxidising mineral acid.

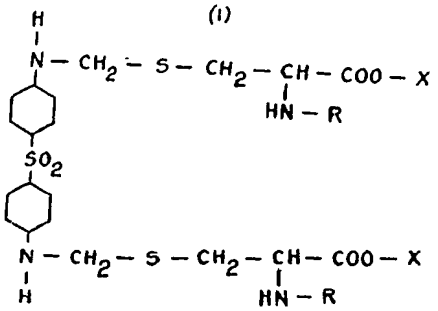
These new derivatives are stable, are of low toxicity and are efficacious on oral, parenteral and intravenous administration for the treatment of streptococcal and pneumococcal infections, especially those of great virulence.

In effect the formation of these new derivatives not only imparts various desirable physical and chemical properties to the parent compound, 4,4¹-diaminodiphenyl sulphone, but accomplishes marked detoxification of it as well.

The products of the present invention may be represented by the following formulas:

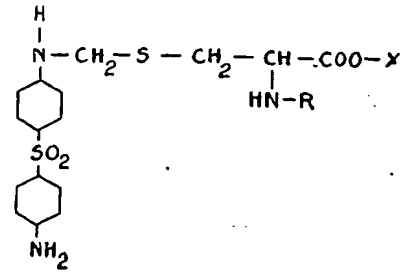
N,N¹-bis-(1-carboxy-1-acylaminoethylthiomethyl) derivatives of 4,4¹-diaminodiphenyl sulphone.

(1)



N-(1-carboxy-1-acylaminoethylthiomethyl) derivatives of 4,4¹-diaminodiphenyl sulphone.

(2)



in which R represents an acyl group preferably of the class comprising those derived from the alkanoic and haloalkanoic acids of less than eight carbon atoms, those derived from the aromatic and heterocyclic carboxylic acids, and those derived from the aromatic sulphonic acids, including *inter alia* the formyl, acetyl, chloroacetyl, -bromopropionyl, benzoyl, nicotinyl, and benzenesulphonyl groups; and X represents a member of the

[*Price* 1/-]

general class of positive ions, consisting of hydrogen, the alkali metals, the normal equivalents of the alkaline-earth metals, the nitrogen hydro-onium ions derived from ammonia, the alkylamines, the alkanolamines and the polymethylenediamines, including ethylene diaminer.

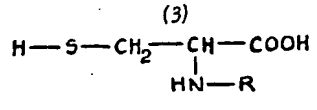
The salts are all freely soluble in water, and in general relatively stable in the solid state. The alkali and alkaline-earth metal salts are very slightly soluble in absolute alcohol, and insoluble in ether and benzene. The acids differ somewhat as to their solubility in water, and in general are both less water-soluble and less stable than are the salts.

The N-formylcysteine is prepared in accordance with the method described in the Journal of Biological Chemistry *106* 689. The other N-acylcysteines are prepared by reacting the corresponding acyl anhydride or acyl chloride with crystine, followed by reduction, in accordance with the method described in Biochemical Journal *25* 614—616 for the preparation of N-acetylcysteine and N-chloroacetylcysteine. Either the acyl chloride or the acyl anhydride may be used as the acylating agent. However, it is preferable to use the acyl anhydride for the N-acylcysteines derived from alkanoic acids, such as N-acetylcysteine, and to use acyl chlorides for the preparation of N-acylcysteines derived from the haloalkanoic acids, such as N-β-bromopropionylcysteine, and from the aromatic and heterocyclic carboxylic acids, such as N-benzoylcysteine and N-nicotinylcysteine.

In carrying out the processes of the present invention, one may in general proceed as follows:

To a solution (or suspension) of 4,4^1-diamino-diphenyl sulphone in a suitable solvent, such as methyl or ethyl alcohol, or ethylene or propylene glycol, or dioxane, one adds either one or two molecular equivalents of formaldehyde, according to whether it is desired to obtan a substitution on one or both of the amino groups; and also add one or two molecular equivalents, depending on the same consideration as before, of an N-acylcysteine of the general formula:

(3)



It is desirable but not necessary to add the formaldehyde before adding the N-acylcysteine; and the N-acylcysteine may be added, and it is desirable to add it, in moderate excess. If desired, the N-acylcysteine may be added directly to N,N^1-dimethylene-4,4^1-diaminodiphenyl sulphone to produce the di-substituted products of formula 1. Non-oxidising mineral acids have been found to be effective catalysts for this condensation.

In either case, the ingredients which are brought together react to produce an acid of the type shown in formula 1 or formula 2 above, with X signifying hydrogen; but that acid is in solution. To obtain such acid in solid form, one adds a large volume of water to precipitate that acid. This precipitation may be facilitated by the addition of sodium chloride or other salting-out reagent. The solid acid thus obtained may be separated from the supernatant liquid in suitable manner, as by filtering, decanting, or centrifuging. As thus obtained it is an amorphous mass. This amorphous mass is washed well with water, and then dried, as in a vacuum desiccator.

Salts may readily be obtained from the acid so produced. To this end, the acid, as represented by formula 1 or formula 2 with X signifying hydrogen, is dissolved in a non-aqueous solvent, suitably in absolute alcohol, and is treated with a solution in the same solvent of a desired base, such as sodium hydroxide or ethoxide, or the hydroxide or the ethoxide of other metals (such for instance as potassium ethoxide, calcium ethoxide, or magnesium ethoxide) or ammonia or an alkylamine, such as methylamine, or an alkanolamine, such as ethanolamine, or a polymethylene diamine, such as ethylene diamine. A salt is formed by the resultant reaction, and that salt usually separates because of its relative insolubility in the solvent used. If precipitation does not occur, or is incomplete, it may be produced or brought to completion by the addition of dry ether or acetone. Thus, when methylamine, ethanolamine, diethanolamine, isopropanolamine, or dry ammonia gas are used the resultant salts are alcohol-soluble, but may be caused to separate from solution by the addition of relatively large quantities (say two to five volumes) of dry ether or acetone, preferably the latter. These salts are very water-soluble (indeed hygroscopic) and are usually obtained in the form of amorphous solids or gums, which may be suitably dried, as *in vacuo*. When the ethylenediamine is used in the proportion of about one mole of diamine to one mole of dicarboxylic acid, the resultant salt separates, at least in part, from alcoholic solution. More complete separation may be effected by the addition of dry ether or acetone. When ethylenediamine is used in the proportion of two or more moles of diamine to one mole

of dicarboxylic acid as represented generically in formula 1, the resultant salt is alcohol-soluble, but may be caused to separate from solution as described above for the ammonium and alkanolamine salts.

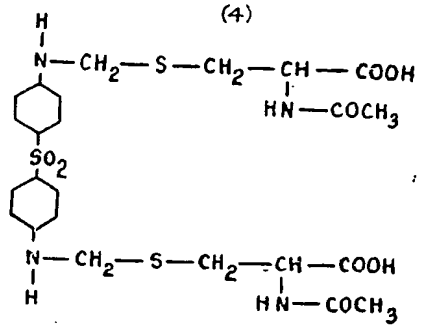
When salts of the disubstituted acid of formula 1 are desired, it is possible to obtain either a mono-salt or a di-salt by substituting the desired basic element or radical in only one or in both of the two carboxyl groups. For example, if it is desired to obtain a mono-salt, an alcohol solution of sodium ethoxide, for instance, is poured into an alcohol solution of the acid, whereupon, with chilling if necessary, the mono-salt (here the mono-sodium salt) precipitates. If it is desired to obtain the di-salt, the simplest way is to reverse the pouring procedure. An alcohol solution of the acid is poured into an alcohol solution of sodium ethoxide (taking sodium as an example); by which procedure the precipitate which forms is the di-salt. In either case, it is desirable to use an amount of the sodium ethoxide which is about double what would be called for on a molecular equivalency basis; although that is not imperative.

When the salts are desired, it is not essential first to isolate the corresponding free acids. To prepare the salts direct the following procedure may be followed: To one molecular equivalent of 4,4¹-diaminodiphenyl sulphone, dissolved and suspended in an anhydrous solvent (suitably absolute ethyl alcohol), is added either one molecular equivalent each of formaldehyde solution and an N-acylcysteine, or two molecular equivalents each of formaldehyde solution and an N-acylcysteine, depending upon whether a salt of an N - (1 - carboxy - 1 - acylaminoethylthiomethyl)-4.4¹-diaminodiphenyl sulphone or of an N,N¹-bis-(1-carboxyl-1-acylaminoethylthiomethyl) - 4,4¹ - diaminodiphenyl sulphone is desired. A small amount of a strong, non-oxidizing acid, suitably hydrochloric acid, is added as catalyst. The total concentration of acid catalyst need not exceed 0.05%. The mixture is then agitated or allowed to stand until complete solution of solid material has been effected. The resultant solution is then chilled and filtered if necessary and is further treated with a suitable base.

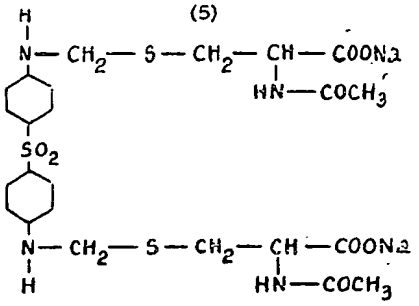
Examples of the general processes are as follows:

EXAMPLE I.

To five grams of 4,4¹-diaminodiphenyl sulphone suspended (with some dissolving) in 25 cc. of 70% alcohol are added 4.5 cc. of formalin (36% formaldehyde) and 6.5 grams of N-acetylcysteine. The mixture is allowed to stand for several hours. It is then treated with sodium carbonate, and the insoluble material then present is removed, as by filtration, and rejected. The filtrate is chilled, and acidified with hydrochloride acid. A pale yellow gum separates. The pale yellow gum is dried in vacuum, desirably over phosphorus pentoxide. This yellow gum is N,N¹-bis-(1 - carboxy - 1 - acetylaminoethylthiomethyl)-4,4¹-diaminodiphenyl sulphone which has the following formula:



This product, represented by formula (4), is then dissolved in absolute alcohol, and the solution is filtered if necessary. To this alcoholic solution, an alcohol solution of sodium hydroxide is added. A precipitate separates, and is collected on a filter and dried *in vacuo*. An analysis for nitrogen showed 8.58% which is in good agreement with the calculated value, 8.72%, required by the following formula:



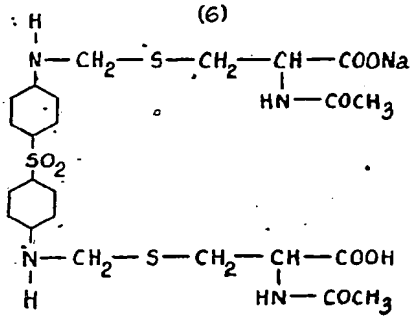
EXAMPLE II.

The process of Example I is repeated through to the production of N,N¹-bis-(1 - carboxy - 1 - acetylaminoethylthiomethyl)-4,4¹-diaminodiphenyl sulphone, shown in formula 4. Mono-substituted and di-substituted salts are then obtained (in better yields than by the process of Example 1) by employing sodium ethoxide in place of sodium hydroxide in the process.

To prepare the mono-sodium salt, one adds about two molecular equivalents of

sodium ethoxide dissolved in absolute ethyl alcohol to an alcohol solution of the N,N¹ - bis - (1 - carboxy - 1 - acetylaminoethylthiomethyl) - 4,4¹ - diaminodiphenyl sulphone. During this addition the entire mixture is chilled to about 5° C. The mono-sodium salt separates at once. It is allowed to stand for a few minutes (say ten to fifteen), and is then collected on a filter, and is dried in vacuum. Analysis for sodium of this salt indicates that only the hydrogen atom of one of the carboxyl groups is replaced by a sodium atom; and a water solution of this sodium salt is acid to litmus. This mono-sodium salt has the following formula:

(6)



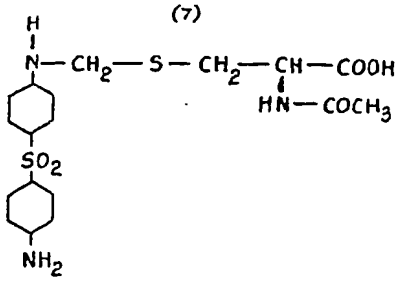
To prepare the di-sodium salt, 4 molecular equivalents of sodium ethoxide are dissolved in absolute alcohol, and the whole is well cooled. To this alcohol solution of sodium ethoxide, one adds an alcohol solution of one mole of the N,N¹-bis - (1 - carboxy - 1 - acetylaminoethylthiomethyl)-4,4¹-diaminodiphenyl sulphone. The di-sodium salt then separates at once, and can be collected on a filter and dried in vacuum. Analysis for sodium of this salt indicates that the hydrogen atoms of both carboxyl groups have been replaced by sodium atoms, and a water solution of this salt is approximately neutral to litmus. This di-sodium salt has the formula 5 above.

Both the mono-sodium salt and the di-sodium salt are effective therapeutic agents.

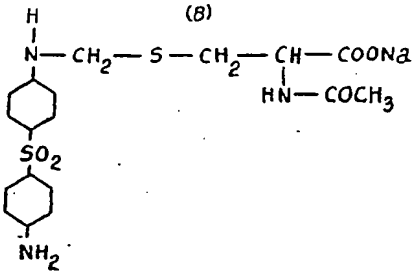
EXAMPLE III.

Examples I and II may be repeated, save that only one-half the quantities of formaldehyde and N-acetylcysteine are used. The resultant intermediate and final products are the mono-substituted 4,4¹-diaminodiphenyl sulphone and its sodium salt, which are represented by the following formulas:

(7)



(8)

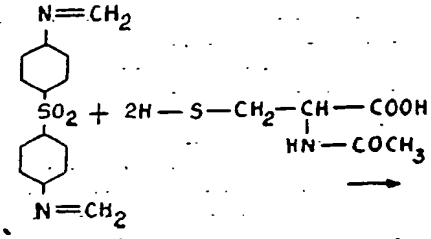


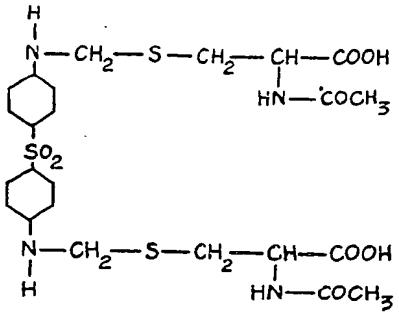
EXAMPLE IV.

The disubstituted acid of Example I may be produced by condensation of the N-acetylcysteine with N,N¹-dimethylene-4,4¹-diaminodiphenyl sulphone. This may be accomplished by the following procedure:

N,N¹ - Dimethylene - 4,4¹ - diaminodiphenyl sulphone, suspended in methyl alcohol, dioxane, ethyl alcohol or other suitable solvent is treated with two (or a slight excess over two) molecular equivalents of N-acetylcysteine, and a small amount of a strong acid, preferably hydrochloric acid, as a catalyst. The total concentration of the acid catalyst need not exceed 0.05% in solution. Instead of hydrochloric acid one may use any non-oxidizing mineral acid or any organic acid which has an ionization constant of about 10^{-3} to 10^{-5}, such as maleic acid. The following reaction takes place:

(9)

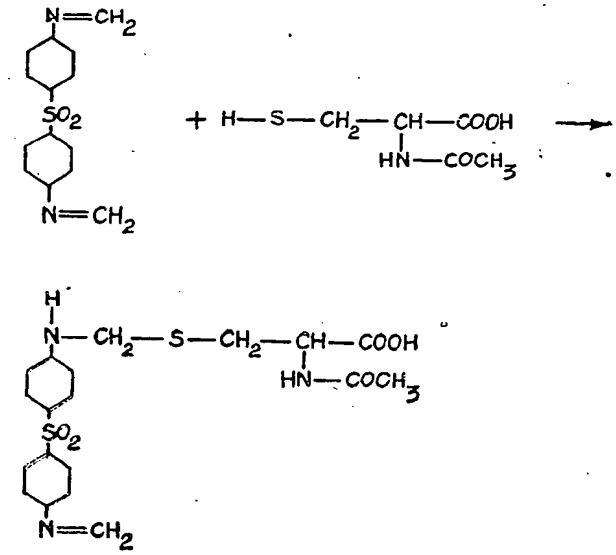




The compound N,N¹-bis-(1-carboxy-1-acetylaminoethylthiomethyl) - 4,4¹ - diaminodiphenyl sulphone, which is thus produced, is in solution. This free acid can be isolated as described as in Example I. The salts of this derivative, for example sodium salt, can be obtained as the salts were produced in Examples I and II.

If instead of two molecular equivalents of N-acetylcysteine only one molecular equivalent is used the reaction is as follows:

(10)



EXAMPLE V.

Examples I, II, III and IV are repeated, save that instead of using N-acetylcysteine, an equivalent quantity is used of either N-β-bromopropionylcysteine, or N-benzoylcysteine, or N-nicotinylcysteine, or N-formylcysteine or N-chloroacetylcysteine.

In Examples I to IV inclusive, the structures as indicated in formulas 4 to 10 inclusive show N-(1-carboxy-1-acylamino-ethylthiomethyl) or N,N¹-bis-(1-carboxy-1-acylamino-ethylthiomethyl) derivatives of 4,4¹-diaminodiphenyl sulphone without any methylol group in the benzene nucleus. It is known that when an aromatic primary amine is treated with formaldehyde in acid solution, some of the formaldehyde tends to condense with the aromatic ring to yield a methylol derivative. It is therefore possible that the products resulting from the practice of the methods described in the examples contain some of the methylol group in the benzene ring. The precise amount of the methylol compounds in the reaction products of each of these examples has not been ascertained.

The salts of the acids described may also conveniently be prepared by treating the alkali metal salts of the required acids with water soluble neutral salts of the required metals.

Having now particularly described and ascertained the nature of our said invention and in what manner the same is to be performed, we declare that what we claim is:—

1. A process of producing new therapeutically effective derivatives of 4,4¹-diaminodiphenyl sulphone having low toxicity and high stability which comprises reacting 4,4¹-diaminodiphenyl sulphone with formaldehyde and with an N-acylcysteine.

2. The process of producing new therapeutically effective derivatives of 4,4¹-diaminodiphenyl sulphone having low toxicity and high stability which comprises reacting an N-acylcysteine with the

product resulting from the interaction of 4,4¹-diaminodiphenyl sulphone and formaldehyde.

3. A process as claimed in claim 1 or 2, in which the reaction takes place in a suitable medium in the presence of a small amount of a non-oxidizing mineral acid.

4. A process as claimed in claim 3 in which the medium is alcohol.

5. A process as claimed in any one of the preceding claims in which the N-acylcysteine is N-acetylcysteine.

6. A process as claimed in any one of the preceding claims in which the reaction product is reacted with a base to form the corresponding salt.

7. A process as claimed in claim 6, in which the reaction product is reacted with the base in a non-aqueous solvent.

8. A process as claimed in claim 6 or 7 in which the base is an alkali metal base.

9. A process as claimed in claim 6, 7, or 8 in which the base is a sodium base.

10. A process as claimed in claim 6, 7, 8, or 9 in which the base is sodium ethoxide.

11. The manufacture of new therapeutically effective products substantially as described with reference to the foregoing Examples.

12. New therapeutically effective mono- and di-N-substituted 4,4¹-diaminodiphenyl sulphones whenever prepared by the methods or processes herein particularly described or by their obvious chemical equivalents.

Dated this 6th day of November, 1940.

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